

REMARKS

Upon entry of the foregoing amendments, Claims 128-143 are pending. Applicants have cancelled Claims 93-116 and 118-127 without disclaimer of, or prejudice to, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability, and reserve the right to prosecute the subject matter of the canceled claims in a continuation or divisional application. Applicants have added new Claims 128-143, which are fully supported by the specification and original claims as filed. Accordingly, the amendments add no new matter. Specifically, support for the amendments can be found at paragraphs 0033, 0044, 0047, 0049, 0063, 0066, 0067, 0070, 0092, 0093, 0099, and Example 1 of the U.S. Patent Application Publication No. 2005/0260174.

Claims 93-116 and 118-127 were rejected in the Office Action mailed February 10, 2009. Applicants respond below to the specific rejections set forth in the Office Action.

Rejections Under 35 U.S.C. § 102

The Examiner has maintained the rejection of Claims 93-116 and 118-127 as allegedly being anticipated under § 102(e) by U.S. Patent No. 6,777,231 to Katz et al. According to the Examiner, Katz et al. teach adipose tissue that contains adipose-derived stem cells. The Examiner states that even though Applicants' claims require a mixture of unprocessed adipose tissue and disaggregated adipose-derived stem cells, "it is unclear that the resultant mixture would be different from a typical adipose tissue sample," as in Katz et al., since upon mixing, the disaggregated cells would "no longer be disaggregated." (Office Action at 3). The Examiner also notes that the amount of added cells is nearly negligible, noting that certain adipose tissue is known to have higher concentrations of cells than others. Thus, the Examiner concludes that the claimed mixtures are anticipated by Katz et al.

The Examiner has also rejected Claims 93-94, 96-105, 107-116 as allegedly being anticipated under § 102(b) by U.S. Patent No. 5,744,360 to Hu et al. The Examiner asserts that Hu et al. teach adipose tissue, which inherently contains adipose-derived stem cells, and maintains that Hu et al. thus anticipates Applicants' claimed composition for the same reasons discussed in connection with the 35 U.S.C. § 102 rejection in view of Katz et al.

Applicants have amended the claims to recite an autologous soft tissue filler and a stable autologous tissue graft that comprises a mixture of:

- (a) adipose tissue that comprises connective tissue and
- (b) a concentrated population of adipose-derived cells comprising adipose-derived stem cells, wherein:

- (1) the amount of said adipose tissue in said autologous soft tissue filler is sufficient to correct a contour defect in a human or the amount of said adipose tissue in said stable autologous tissue graft is sufficient to support a reconstructive tissue graft in a human;

- (2) said concentrated population of adipose-derived cells comprising adipose-derived stem cells are substantially disaggregated in said mixture; and

- (3) said concentrated population of adipose-derived cells comprising adipose-derived stem cells are in an amount sufficient to support prolonged survival of said autologous soft tissue filler/stable autologous tissue graft or said concentrated population of adipose-derived cells comprising adipose-derived stem cells are in an amount sufficient to promote improved vascularity of said autologous soft tissue filler/stable autologous tissue graft.

The new claims presented herein require a composition that is a mixture having an amount of adipose tissue sufficient to provide a soft tissue filler or tissue graft that corrects contour defects in a human or supports a reconstructive tissue graft and an amount of a concentrated population of adipose-derived cells comprising adipose-derived stem cells sufficient to support prolonged survival or improved vascularity of said filler/graft with the *proviso* that the concentrated population of adipose-derived cells comprising adipose-derived stem cells in the mixture are substantially disaggregated. Applicants respectfully submit that the claimed compositions are not the same as lipoaspirate, purified adipose derived stem cells, or adipose tissue and, specifically, are not the same as the compositions prepared by Katz et al. and/or Hu et al.

Applicants note that although different samples of adipose tissue may vary in the amount of adipose-derived stem cells, the viable adipose-derived stem cells in the sample are substantially embedded in the connective tissue (i.e., the viable adipose-derived stem cells are not disaggregated and are not present in numbers sufficient to support prolonged survival or improved vascularity of said filler/graft). As adipose tissue is removed from the body, the disaggregated cells that may accompany the sample are damaged or lysed in the processing steps and/or are removed by the washing of the tissue. That is, once adipose tissue is removed from the body and washed (e.g., following the procedures described by Katz et al. or Hu et al.), the remaining viable adipose derived stem cells are embedded in the adipose tissue matrix and the amount of disaggregated adipose-derived cells comprising adipose-derived stem cells on the adipose tissue are in an amount that is not sufficient to support prolonged survival or improved vascularity of the tissue sample.

Applicants note that conventional cell suspensions that contain adipose-derived stem cells (e.g., the purified adipose derived stem cells prepared by Katz et al.) do not contain an amount of adipose tissue sufficient to correct a contour defect in a human or to support a reconstructive tissue graft in a human. That is, the trace amount of adipose tissue that may contaminate the Katz preparation is insufficient to correct a contour defect or to support a reconstructive tissue graft in a human. Accordingly, Katz et al. does not anticipate the present claims.

The presently claimed compositions embody a mixture of adipose tissue (in an amount sufficient to correct a contour defect or to support a reconstructive tissue graft in a human) and a concentrated population of adipose-derived cells comprising adipose-derived stem cells, which remain substantially disaggregated. The Examiner has asserted that upon mixing, the disaggregated cells would no longer be disaggregated. Applicants present evidence that this is not the case (*see Exhibit A, a color photograph available upon request*). **Exhibit A** compares a diagram of a conventional adipose tissue graft ("Conventional Graft") and a diagram of the claimed composition ("Celution Graft"). **Exhibit A** also shows a picture of the claimed composition that has been fluorescently- labeled to show the presence and location of the adipose-derived stem cells (bright spots on the figure). Note, the fluorescent labeling indicates

that the adipose-derived stem cells in the Celution Graft remain disaggregated and located at the surface of the graft. Because the presently claimed compositions require an amount of adipose tissue sufficient to correct a contour defect or to support a reconstructive tissue graft in a human in addition to the disaggregated concentrated population of adipose-derived stem cells, the claimed compositions are different than adipose tissue (as exemplified by Hu et al.) and purified stem cells (as exemplified by Katz et al.). Further, the claimed compositions are different than the preparations of Hu et al. and/or Katz et al. because the claims now require that the mixture supports prolonged survival or improved vascularity of said autologous soft tissue filler/stable autologous tissue graft. As discussed in greater detail below, adipose tissue by itself does not support prolonged survival or improved vascularity of a tissue graft; whereas, the claimed compositions were found to support prolonged survival and improved vascularity of tissue grafts.

Applicants submit that the claimed compositions are also different than lipoaspirate preparations that include adipose-derived stem cells (*see Exhibit B*). **Exhibit B** shows that the claimed compositions ("Celution") have 28-fold more free colony forming unit fibroblast/ml (CFU-F) and 62-fold more preadipocytes/ml than lipoaspirate ("centrifuged"). **Exhibit C** shows that that the claimed compositions ("Celution") have 105-fold more CD34+/CD31- cells/ml and 63-fold more CD34+/CD31+ cells/ml than lipoaspirate ("centrifuged"). Accordingly, Applicants respectfully submit that the claimed compositions are different than adipose tissue, purified adipose-derived stem cells, and lipoaspirate because the claimed compositions have an amount of adipose tissue sufficient to correct a contour defect or to support a reconstructive tissue graft in a human and an amount of disaggregated, concentrated population of adipose-derived cells comprising adipose-derived stem cells sufficient to support prolonged survival or improved vascularity of said autologous soft tissue filler/stable autologous tissue graft. Accordingly, Applicants request that the rejections under 35 U.S.C. § 102 be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of Claims 93-94, 96-105, 107-116 and 118-127 as allegedly being unpatentably obvious over Katz et al., or U.S. Patent No. 6,200,606 to Peterson et al. According to the Examiner, both Katz et al. and Peterson et al. teach

compositions comprising adipose-derived stem cells in a complex mixture and substantially free of other cells and tissues. The Examiner argues that the reference teach “how and why to purify the desired cells,” and states that “any difference in the claimed compositions and those taught by the [cited] art would be only a matter of the concentration of the cells and tissues contained therein.” (Office Action at 5). The Examiner concludes that “unless there is evidence indicating such concentration is critical,” this feature will not support the patentability of Applicants’ claimed invention.

In light of the present amendments, Applicants respectfully submit that of Katz et al. and Peterson et al. do not make obvious the currently claimed invention. Applicants note that the claims now require an amount of adipose tissue in said filler/graft that is sufficient to correct a contour defect or to support a reconstructive tissue graft in a human and Katz et al. and Peterson et al., describe compositions comprising adipose derived stem cells substantially free of other cells and tissues. Applicants also note that the present claims require that the embodied compositions contain an amount of disaggregated, concentrated population of adipose-derived cells comprising adipose-derived stem cells sufficient to support prolonged survival or improved vascularity of the filler/graft, which is lacking from the description provided by Katz et al. and Peterson et al.

Applicants further submit that the aspects that set their invention apart from the prior art led to the unexpected results that the claimed soft tissue filler and tissue graft supported prolonged survival and improved vascularity of the filler/graft. As previously set forth during the prosecution of this application (e.g., *see* the declaration by Dr. John Fraser), Applicants have shown that graft weight and vascularity of fat implants are improved by mixing unprocessed adipose tissue and isolated preparations of adipose-derived cells comprising stem cells and progenitor cells (*see also Example 1 of the specification*). As set forth in Dr. Fraser’s declaration, the results of the studies in Example 1 of the instant specification were confirmed in a human clinical trial, wherein twenty-one (21) female patients underwent 25 stem cell augmented reconstructions. Adipose tissue was harvested by lipoaspiration, divided into two equal portions; one portion, referred to as “Fat A”, was reserved for processing in the cell processing

system described in the instant patent application to extract, wash and concentrate adipose derived stem cells; the other portion, "Fat B", was used as the primary filler material. Concurrent to the processing of "Fat A", "Fat B" was irrigated to remove any blood, and the remaining adipose tissue, which had been fragmented into numerous 2 - 5 mm fragments by the lipos aspiration procedure, was enriched with concentrated adipose-derived stem cells out of the cell processing device by gentle mixing immediately prior to the autologous transplantation procedure. Subsequently, the autologous adipose derived stem and regenerative cell (ADRC) enhanced fat graft was provided to the patient and the grafts remained intact for the longest time period analyzed (eighteen months).

In follow-up experiments, Applicants developed a murine fat transplantation model using the subcutaneous space on the skull as the recipient site for fat grafts. In this model, fat tissue was harvested from the mouse inguinal fat pads and finely minced. Each 60-mg fat graft was mixed with either saline (Fat-only group) or 5×10^6 ADRCs freshly isolated from ROSA26 mice (Fat+ADRCs group), which contain *LacZ* as a transgene, and subsequently injected into the subcutaneous space on the skulls of host mice. The grafts were extirpated and weighed six and nine months after transplantation. At the time of harvesting, there was visibly more grafted fat retained on the skull in the Fat+ADRCs group than in the Fat-only group (see **Exhibit D**). Analysis of weight showed that the mean graft weight in the Fat+ADRCs group was approximately two-fold higher than that of the Fat-only group at both six months (15.02 ± 1.38 vs. 7.55 ± 1.75 mg, $p=0.019$, $N=10$ and 11 in the Fat+ADRCs and Fat-only groups, respectively) and at nine months (15.06 ± 3.37 vs. 7.31 ± 1.13 mg, $p=0.034$, $N=12$ and 13 in the Fat+ADRCs and Fat-only groups, respectively), demonstrating ADRCs could indeed improve the long-term retention of the transplanted fat (see **Exhibit D**). Accordingly, the claimed composition supports prolonged survival of said autologous soft tissue filler/stable autologous tissue graft but adipose tissue alone (e.g., the preparation as taught by of Hu et al.) does not.

Neovascularization as evidenced by capillary density in the grafts was also analyzed. Immunostaining of CD31, an endothelial cell marker, revealed that grafts from the Fat+ADRCs group had a significantly higher mean capillary density than those from the Fat-only group at

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both six and nine months (*see Exhibit E*). Accordingly, the claimed compositions promote improved vascularity of said autologous soft tissue filler/stable autologous tissue graft but adipose tissue alone (e.g., the preparation as taught by of Hu et al.) does not. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

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CONCLUSION

In view of the above amendments and remarks, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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